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Review article

Therapeutic approach to CML in TKI era

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Abstract

Chronic myeloid leukemia is a cancer that affects the cells of the bone marrow. These effected cells can grow and divide rapidly and spill into other parts of the body. It is relatively prevalent in the United States with 14% of cancer diagnoses being for CML. Immunotherapy is a new way to fight this cancer. The new era in the management of CML has started with the advent Tyrosine kinase inhibitors. This therapy stimulates one's own immune system to fight the malignant tumor. We can classify the immunotherapeutics into TKI therapies and non TKI therapies broadly. In this paper, we discussed the causes, epidemiology, and potential immunotherapeutic techniques to treat CML.

Keywords: Chronic Myeloid Leukemia; Cancer; Immunotherapy

Abbreviations

CML: Chronic Myeloid Leukemia;
TKI: Tyrosine Kinase Inhibitors;
DLI: Donor Lymphocyte Infusion;
VEGFR: Vascular Endothelial Growth Factor Receptors ;
FGFRs: Fibroblast Growth Factor Receptors;
Ph: Philadelphia

Introduction

According to the American Cancer Society, in 2014 there wereapproximately 5,980 new cases of Chronic Myeloid Leukemia (CML) diagnosed in the United States (US). In the same year, 810 deaths were also reported [1]. This form of leukemia is highly prevalent in western countries.

CML constitutes 14% of all forms of leukemia [2]. In 2012, the age-standardized rate of incidence of CML was 1.6 per 100,000 people and in 2009, the overall five-year survival rate was 59% in the US. The five-year survival rate for CML has nearly doubled from 31%, for people diagnosed in the early 1990s, to 60% for those diagnosed between 2004 and 2010. This is mostly due to advanced targeted therapies such as Imatinib and next generation tyrosine kinase inhibitors. Moreover, survival statistics are measured in five-year intervals and may not represent all of the recent significant advances made in the treatment and diagnosis of CML. In one study of patients with CML who were consistently taking the drug Imatinib, researchers found that 90% lived at least five years [1].

The male-to-female ratio of incidence is 1.4:1, with a predominance of male over female and higher incidence observed in between the age group of 40 to 60 years.[3] The etiology of CML is unknown. Very few results correlate CML to hereditary factors. The children of patients with CML do not have a higher incidence of CML than the general population. These results suggest that CML is not hereditary, but

an acquired disorder. Causality associated with radiation and CML is questionable. The symptoms of CML include: lethargy, night sweats, loss of weight, and abdominal fullness [4].

CML advances from a chronic phase, which is benign, to a catastrophic blast crisis that has a resemblance to acute leukemia. CML occurs when the genetic material is swapped between chromosome 9 and chromosome 22 (Philadelphia chromosome), which results in the Bcr-Abl fusion gene. This fusion gene, results in an abnormal protein that makes way for unrestrained activity of tyrosine kinase (TK) [5].

Considerable progress has been made in the understanding of the immunology of CML. This has raised hopes that this disease may be curable by combination of targeted chemotherapy and immunotherapeutic approaches. Recent data indicating that the p210bcr-abl protein does not carry the immunodominant epitope led to recognition of an ever increasing number of other immunogenic proteins in CML cells. Following are the various immunotherapeutic approaches that are available and are under clinical trials.

A. Immunotherapeutics for the management of CML:

a. TK Inhibitors:

A tyrosine kinase inhibitor (TKI) is a pharmaceutical drug that inhibits tyrosine kinases. Tyrosine kinases are enzymes responsible for the activation of many proteins by signal transduction cascades. The proteins are activated by adding a phosphate group to the protein (phosphorylation), a step that TKIs inhibit. TKIs have substantially improved outcomes in chronic myelogenous leukemia.

1. Imatinib[6]: It is the first TK inhibitor that has been introduced and approved as a therapy for newly diagnosed adult and pediatric patients with the Philadelphia chromosome positive for chronic myeloid leukemia (Ph+ CML) in the chronic phase. Imatinib binds to an intracellular pocket located within the TKs, thereby inhibiting ATP binding and preventing phosphorylation and the subsequent activation of growth receptors and their downstream signal transduction pathways. This agent inhibits TK encoded by the Bcr-Abl oncogene as well as receptor TKs encoded by the c-kit and platelet-derived growth factor receptor (PDGFR) oncogenes. Inhibition of the Bcr-Abl TK results in decreased proliferation and enhanced apoptosis in malignant cells of Philadelphia-positive (Ph+) hematological malignancies such as CML and ALL

The major adverse events associated with Imatinib are thrombocytopenia, neutropenia, anemia, edema, severe hepatotoxicity, prolonged QT interval, cardiac dysfunctions, pulmonary arterial hypertension, embryo fetal toxicity, hypothyroidism, diarrhea, vomiting, musculoskeletal pain, headache, skin rash, fatigue, and nausea, which has been reported less frequently.

2. Dasatinib[7]: It is a synthetic small molecule-inhibitor of SRC-family protein-tyrosine kinases. Dasatinib binds to and inhibits the growth-promoting activities of these kinases. Because of its less stringent binding affinity for the Bcr-Abl kinase, Dasatinib has been shown to overcome the resistance to Imatinib of CML cells harboring Bcr-Abl kinase domain point mutations. SRC-family protein tyrosine kinases interact with a variety of cell-surface receptors and participate in intracellular signal transduction pathways; tumorigenic forms can occur through altered regulation or expression of the endogenous protein and by way of virally-encoded kinase genes. It is also indicated for the treatment of adults with Chronic Phase (CP) CML with resistance or intolerance to prior therapy, including Imatinib.

Very common adverse effects are infections (including bacterial, viral, fungal, non-specified), myelosuppression (including anemia, neutropenia, thrombocytopenia), diarrhea, vomiting, nausea, abdominal pain, pleural effusion, dyspnea, skin rash, musculoskeletal pain and hemorrhage.

3. Ponatinib[8]: It is a an orally, bioavailable, multi-targeted receptor tyrosine kinase (RTK) inhibitor with potential anti-angiogenic and antineoplastic activities. Ponatinib inhibits unmutated and all the mutated forms of Bcr-Abl, including T315I, which is the highly drug therapy-resistant missense mutation of Bcr-Abl. This agent also inhibits other TKs, including those associated with vascular endothelial growth factor receptors (VEGFRs) and fibroblast growth factor receptors (FGFRs); in addition, it inhibits the TK receptor TIE2 and FMS-related tyrosine kinase receptor-3 (Flt3). RTK inhibition by ponatinib hydrochloride may result in the inhibition of cellular proliferation and angiogenesis and may induce cell death. Bcr-Abl is a fusion TK encoded by the Philadelphia chromosome.

The US FDA approved Ponatinib in 2012, but temporarily suspended sales on October 31, 2013 because of "the risk of life-threatening blood clots and severe narrowing of blood vessels". This suspension was partially lifted on December 20, 2013 with Ponatinib being issued revised prescribing information. In place was a new "Black Box Warning" and a "Risk Evaluation and Mitigation Strategy" to better evaluate the risks and benefits of using the drug.

The indications are limited to:

• Treatment of adult patients with T315I-positive CML (CP, accelerated phase, or blast phase) or T315I-positive Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL).

• Treatment of adult patients with CP, accelerated phase, or blast phase CML or Ph+ ALL for whom no other Tyrosine Kinase Inhibitor (TKI) therapy is indicated.

The major warnings are arterial thrombosis, hepatotoxicity, congestive heart failure, pancreatitis, fluid retention, cardiac arrhythmias, myelosuppression, Tumor Lysis Syndrome: Compromised Wound Healing and Gastrointestinal Perforations and Embryo-fetal toxicity. The adverse effects include thrombocytopenia, constipation, arthralgia, nausea, pyrexia, anemia and lymphopenia.

4. Nilotinib[9]: It is indicated as a therapy for the treatment of newly diagnosed adult patients with Ph+ CML in the chronic phase. Nilotinib is an orally bioavailable, aminopyrimidine-derivative Bcr-Abl TK inhibitor with antineoplastic activity designed to overcome Imatinib resistance. Nilotinib binds to and stabilizes the inactive conformation of the kinase domain of the Abl protein of the Bcr-Abl fusion protein, resulting in the inhibition of the Bcr-Abl-mediated proliferation of Ph+ CML cells. This agent also inhibits the receptor TKs platelet-derived growth factor receptor (PDGF-R) and c-kit, a receptor TK mutated and constitutively activated in most gastrointestinal stromal tumors (GISTs). With a binding mode that is energetically more favorable than that of Imatinib, Nilotinib has been shown to have an approximate 20fold increased potency in kinase and proliferation assays compared to Imatinib.

It is also indicated for the treatment of CP and accelerated-phase Ph+ CML in adult patients resistant or intolerant to prior treatment, that included Imatinib. The effectiveness of Nilotinib in this subgroup of patients is based on hematologic (blood-related) and cytogenetic (chromosome-related) response rates. There are no controlled trials demonstrating a clinical benefit, such as improvement in disease-related symptoms or increased survival.

The major warnings include prolonged QT interval, sudden death, myelosuppression, ischemic heart disease, pancreatitis, hepatotoxicity, electrolyte abnormalities, hepatic impairment, tumor lysis syndrome, and embryo-fetal toxicity. The adverse effects are nausea, skin rashes, headache, weakness, vomiting, diarrhea, cough, constipation, myelosuppression, thrombocytopenia, neutropenia and anemia.

5. Bosutinib [10]: It is a kinase inhibitor, indicated as a therapy for adult patients with chronic, accelerated, or blast phase Ph+ CML, with resistance or intolerance to prior therapy. Bosutinib is a synthetic quinolone derivative and dual kinase inhibitor that targets both Abl and Src kinases with potential antineoplastic activity. Unlike Imatinib, Bosutinib inhibits the autophosphorylation of both Abl and Src kinases, resulting in the inhibition of cell growth and apoptosis. Because of the dual mechanism of action, this agent may have activity in resistant CML disease, other myeloid malignancies and solid tumors. Abl kinase is upregulated in the presence of the abnormal Bcr-Abl fusion protein, commonly associated with CML. Overexpression of specific Src kinases is also associated with the Imatinib-resistant CML phenotype.

Warnings are gastrointestinal toxicity, myelosuppression, hepatotoxicity, edema, renal toxicity, and embryo-fetal toxicity. The adverse effects include: diarrhea, nausea, vomiting, skin rashes, abdominal pain, pyrexia, weakness, thrombocytopenia, and anemia.

B. Non TKI based therapeutic approaches:

1. Farnesyl Transferase Inhibition:
Farnesyl transferase inhibitors enhance the level of caspase 3, which results in apoptosis. Apoptosis occurs by a series of events, which are triggered by abnormal CDK2 phosphorylation, which changes the conformation of BAX protein, mitochondrial cytochrome c release, swelling of mitochondria and caspase pathway activation. According to a study done by Copland, et al., BMS215662 exhibited cytotoxicity against the cells that were non-proliferative in nature. It is a farnesyl transferase inhibitor and with Imatinib or Dasatinib, it eliminates Ph+ primitive cells. [13]

2. Inhibition of Autophagocytosis:
On the initiation of the process of autophagy, LC3 enzyme is converted from a cytosolic form to a membrane bound form. There is a reduction in the size and increase in cytoplasmic vacuoles in the cells of CML. The same effect is seen during deprivation of growth factors.[14] These cells are the suitable candidates for autophagocytosis or autophagy, which is a response shown by the body for the shortage of nutrients. Dasatinib promotes this conversion of LC3 and hence, stimulates autophagy. This made the basis for combining a TKI, which would eliminate mature cells, along with an inhibitor of autophagy like chloroquine. This would wipe off primitive CML cells.

3. CXCR4 Inhibition:
CXCR4 is a chemokine generated by stromal cells that regulates the process of chemotaxis of CD34+ progenitor cells. This helps in placing the progenitor cells into the microenvironment of the bone marrow.[15] The receptor of SDF1 (CXCL12), CXCR4 is blocked by Bcr-Abl. Imatinib re-establishes the expression of CXCR4, which transfers the CML cells to the bone marrow. [16] This results in cell cycle arrest at G0/G1 phase, inhibits the proliferation, and enhances the survival in dormant state, which makes CML cells resistant to TKI therapy. Hence, CXCR4 inhibitors, like plerixafor, might help to take off this resistance. The combination of TKIs with CXCR4 inhibitors may improve the treatment of CML.

4. Hedgehog (Hh) Signaling Inhibitors:
This pathway plays an important role in the embryonic development and regulates remodeling of chromatin, cell cycle control, and survival.[17] Gli-1 and Gli-2, which are Hh effectors, are highly expressed in CML cells.[18] LDE225, along with Nilotinib lowers the potential of CML cells to form clones.[19]

5. IL-1 Receptor Accessory Protein (IL1–RAP):
In primitive CML cells, the upregulation of IL1–RAP is observed as compared to the healthy cells.[20] It is the first surface marker that has the potential to differentiate between various strains of Bcr-Abl1 cells. Thus, this marker can act as a target for antibodies and eliminate Ph+CML cells. One of the examples for the same is KMP1 antibody that is cytotoxic in nature and specifically kills primitive CML cells.

C. Use of Stem Cell Transplantation:

Mainly, there are two forms of stem cell transplantation: allogeneic stem cell transplantation, which is used as a treatment therapy for some of the CML patients, and autologous stem cell transplantation, which is not widely used in the management of CML.

1. Allogenic Stem Cell Transplantation [21]: It is a technique by which the stem cells of the donor are infused into the patient. Currently, it is a widely used therapy for the treatment of CML. However, the decision to use this transplantation method has become quite complex as many patients exhibit an appreciable response to the TKI therapy. Although the frequency of cure rates is quite high for some of the CML patients, TKIs show an effective control over the disease for long duration of time and maintain a better quality of life as compared to the transplantation.

Initially the patient who has to undergo transplantation is subjected to drug therapy to induce remission. In advanced phases, the objective may be to return to the chronic-phase CML. After the drug therapy, the patients are subjected to the high-dose chemotherapy, followed by transplant. Using this approach, the chances of successful remission after transplantation are quite high, considering that the drugs show minimal side effects.

Various factors that should be kept in consideration while selecting a patient that can be subjected to transplantation include:

1. Age of the patient.
2. General health of the patient.
3. Current CML phase.
4. Response to prior TKI therapy.
5. Well-matched donor availability.

This transplantation method is recommended for the patients having T315I mutation, which is unresponsive to the TKI therapy. Although the transplantation is reported to be more successful in patients of younger age, there is no specific age group up to which the stem cell transplantation may be used. Various risk factors associated with transplantation are:

1. Mortality: Approximately 20% of the patients, who undergo transplantation, died within the duration of two years due to complications.

2. Chronic toxicities are experienced by the patients, who are cured. In some cases, these toxicities can be debilitating.

Approximately, 70% of the patients with CML are cured by allogeneic stem cell transplantation.

2. Donor Lymphocyte Infusion (DLI) [22]: It is a procedure in which the relapsed patients post-transplantation are given lymphocyte infusion, which is derived from the original stem cell donor. This might result in a more intense immune reaction against the CML cells of the recipient. It is found to be more effective in patients with relapse in chronic phase as compared to the advanced phase.

The major side effect of this therapy is graft-versus-host disease. It happens when the infused cells or the cells from the donor consider the recipient's cells as a foreign agent and attacks them. The side effects are potentially serious. However, there are still appreciable results from DLI in some patients.

3. Autologous Stem Cell Transplantation: In this technique, the stem cells are obtained from the person's own bone marrow or the blood. However, this technique is not widely used in the patients with CML. The reason might be the limited benefits of this technique, as reported from long-standing studies.

Conclusion

CML arises from the hematopoietic stem cells in the bone marrow. It is a rare form of cancer and makes up only 14% of all the types of leukemia. The incidence is more in males as compared to females. Targeted therapy has proven to be effective in the treatment of CML. Our success in treating CML is increasing and advancing. Various TK inhibitors are FDA approved immunotherapeutic agents, available for CML. The complete perspective of immunotherapy treatment has not been realized and/ or utilized. Proper preclinical and clinical designs are the important pillars in understanding the future of immunotherapy in treating cancer patients.

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